



TITLE:

# Evaluation of dynamic tumour tracking radiotherapy with real-time monitoring for lung tumours using a gimbal mounted linac.

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1    **Title:**

2    Evaluation of dynamic tumour tracking radiotherapy with real-time monitoring for lung tumours using a  
3    gimbal mounted linac

4

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26

27 This paper consists of 21 pages and 2 tables. There are 2 supplementary figures.

28

29 **Running head:**

30 Dynamic tracking with real-time monitoring

31

32 **Keywords:** stereotactic body radiotherapy; lung cancer; dynamic tumour tracking; real-time monitoring;  
33 feasibility study

34

35    **Abstract:**

36    **Purpose:** To evaluate feasibility and acute toxicities after dynamic tumour tracking (DTT) irradiation  
37    with real-time monitoring for lung tumours using a gimbal mounted linac.

38    **Materials and Methods:** Spherical gold markers were placed around the tumour using a bronchoscope  
39    prior to treatment planning. Prescription dose at the isocentre was 56 Gy in 4 fractions for T2a lung  
40    cancer and metastatic tumour, and 48 Gy in 4 fractions for the others. Dose-volume metrics were  
41    compared between DTT and conventional static irradiation using in-house developed software.

42    **Results:** Of twenty patients enrolled, DTT radiotherapy was successfully performed for 16 patients,  
43    except 4 patients who coughed out the gold markers, one who showed spontaneous tumour regression,  
44    and one where the abdominal wall motion did not correlate with the tumour motion. Dose  
45    covering 95% volume of GTV was not different between the two techniques, while normal lung volume  
46    receiving 20 Gy or more was reduced by 20%. A mean treatment time per fraction was 36 minutes using  
47    DTT. With a median follow-up period of 13.2 months, no severe toxicity grade 3 or worse was observed.

48    **Conclusions:** DTT radiotherapy using a gimbal mounted linac was clinically feasible for lung treatment  
49    without any severe acute toxicity.

50

51

## 52     **Introduction**

53     Lung cancer is the leading cause of cancer-related deaths in most countries, including the US[1] and  
54     Japan[2]. There have been two trends in lung cancer in recent years. The first is the shift in the patient  
55     population to older ages[1,2], and the second is the gradual increase in the ratio of early stage lung  
56     cancer[3,4]. Thus, development of a new treatment modality that is appropriate for elderly patients with  
57     early stage lung cancer is desirable.

58     Stereotactic body radiotherapy (SBRT) was developed as a new treatment modality for early stage lung  
59     cancer in the late 1990s. Many retrospective studies and several multi-institutional prospective trials  
60     have demonstrated that excellent local control is obtained by SBRT, with acceptable toxicity[5–7]. Thus,  
61     SBRT is now an important treatment option for patients with early stage non-small-cell lung cancer who  
62     are medically inoperable and those who are elderly and relatively unfit for surgery.

63     The next innovation expected for lung SBRT is four-dimensional (4D) radiotherapy, which can cope  
64     with tumour movement. The lung expands periodically according to respiration and a lung tumour  
65     moves mainly in the craniocaudal direction. The amplitude of craniocaudal tumour motion is around 1  
66     cm in mean, but can be 3–4 cm in some patients[8]. When the whole trajectory of a moving tumour is  
67     included in the irradiation field, larger volumes of healthy tissues are irradiated. The latter leads to a risk  
68     of toxicity[9–11], and accordingly, that might limit the indication of SBRT to smaller tumours. A new 4D

irradiation technique that permits delivery of a dose to the tumour and limiting that to normal tissues by coping with respiratory motion, may have the potential to improve the outcomes and to expand the indications of SBRT.

The Vero4DRT (formerly called the MHI-TM2000; Mitsubishi Heavy Industries Ltd., Tokyo, Japan, and BrainLab AG, Feldkirchen, Germany)[12] has two special features that allow dynamic tumour tracking (DTT) with real-time monitoring. One is two sets of kilovoltage (kV) x-ray imagers, that can monitor the three-dimensional position of the tumour in real-time via implanted fiducial markers, and the other is a gimbal mounted linac, enabling DTT. Extensive evaluation of the characteristics of this DTT system demonstrated high accuracies in treatment delivery to a moving target[13–17]. Previous experimental validation offered the required confidence for clinical implementation of DTT treatment of lung tumours. The purpose of this study was to evaluate feasibility and acute toxicities after DTT radiotherapy with real-time monitoring in SBRT for lung cancers using the Vero4DRT system.

## Materials and Methods

### *Patients*

Eligibility criteria were as follows: (1) a single lung tumour with a diameter of 50 mm or less, (2) no nodal or distant metastasis, (3) respiratory tumour movement of 5 mm or more, (4) age of 20 years or

above, (5) performance status of 0-2, (6) arms could be held over the head for 30 min or more, (7) doses to adjacent organs not exceeding the pre-determined constraints, which were the same as in the Japan Clinical Oncology Group protocol 0403[18], and (8) written informed consent. This study was approved by the institutional review board. It was registered with the UMIN Clinical Trials Registry in Japan (UMIN000005324).

#### *Pre-planning procedures*

Prior to treatment planning, spherical gold markers with a diameter of 1.5 mm (FMR-201CR; Olympus Medical Systems, Tokyo, Japan) were placed around the tumour under bronchoscopic guidance as an internal surrogate for the tumour position. Treatment planning was carried out 1 week after insertion of the gold markers. At least 3 markers were required for the DTT irradiation to be performed.

On the simulation day, the patient was fixed in a supine position with both arms raised using an individualized vacuum pillow (BodyFIX; Elekta AB, Stockholm, Sweden, or ESFORM; Engineering System, Matsumoto, Japan). Ten respiratory phases of 4D CT were acquired in axial cine mode using a 16-slice CT scanner (LightSpeed RT16 or BrightSpeed Elite; GE Healthcare, Little Chalfont, UK) and a real-time positioning management system (Varian Medical Systems, Palo Alto, US). Immediately after the 4D CT scan, a breath-hold CT scan was also acquired at the end of exhalation. The breath-hold CT

103 was sent to iPlan RT image (ver. 4.1; BrainLab AG) as a reference image. The coordinate for each phase  
104 image from the 4D CT was modified so that its centroid of the fiducial markers was matched with that in  
105 the breath-hold CT. Then, the 10 phase images were fused onto the breath-hold CT. After the CT scan,  
106 the patient was moved to the Vero4DRT to perform a 4D modelling[14], which correlates the external  
107 abdominal motion and the internal fiducial motion. The purpose of the modelling was to estimate the 4D  
108 modelling error and the peak-to-peak amplitude of tumour motion.

109

110 *Treatment planning*

111 Gross tumour volumes (GTVs) were delineated on the breath-hold CT and 10 phase images. An internal  
112 target volume for tracking (ITV) was defined as a composite of the eleven GTVs from the breath-hold  
113 CT and the 10 phase images (Supplementary Fig. 1). Because the phase images were registered based on  
114 the marker centroid, the ITV was supposed to compensate for tumour deformation and uncertainty in the  
115 positional relationship between the tumour and fiducial makers during respiration[19]. Planning target  
116 volume (PTV) for tracking was defined as the ITV plus setup error and additional margins to  
117 compensate the 4D modeling error, baseline drift of the abdominal position, and mechanical errors of the  
118 system. The setup error was estimated to be 2.5 mm in each direction as an inter-fraction positional  
119 variation between the fiducials and the tumour[19]. A margin for the 4D modelling error was defined as



120 a mean plus 2 times of standard deviation in the 4D model on the simulation day. A margin for the  
121 baseline drift was estimated as 10% of the tumour motion amplitude. The mechanical errors were  
122 defined as 0.5 mm[12]. The PTV margin was defined as a linear sum of these errors. At least 5 mm was  
123 required for the margin.

124 Monitor units (MUs) for the treatment beams were calculated using the X-ray voxel Monte Carlo  
125 algorithm in iPlan RT dose (ver. 4.5.1; BrainLab AG) on the breath-hold exhale CT. The prescription  
126 dose was 48 Gy in four fractions for stage IA lung cancer, and 56 Gy in four fractions for stage IB lung  
127 cancer and metastatic lung tumour. This dose was prescribed at the isocentre. We typically arranged  
128 seven beams: four non-coplanar and three coplanar beams. 6-MV x-ray beams were collimated to the  
129 PTV plus 5-mm margin with a multi-leaf collimator. A static SBRT plan with non-tracking beams, based  
130 on the motion-encompassing method[8], was also prepared as a backup if DTT irradiation could not be  
131 achieved for some reason. Dose distributions were evaluated with an in-house developed software that  
132 allows 4D dose calculation considering with the gimbal mounted linac[20]. The calculated dose  
133 distributions for the 10 phase CT images were accumulated into the exhale breath-hold CT with  
134 deformable image registration using MIM Maestro (ver. 5.2; MIM Software Inc., Cleveland, OH). If the  
135 dose-volume metrics in the tracking plan were diagnosed to be superior to those in the static plan, the  
136 patient underwent DTT irradiation.

137

138 *Irradiation of treatment beams*

139 First, the patient was laid on the pre-formed vacuum pillow. Set-up error was corrected for bony  
140 structures using the ExacTrac X-ray system. Second, a 4D model was built to correlate the infra-red  
141 markers on the abdomen with the internal fiducial markers. Then, irradiation could start in dynamic  
142 tracking mode with the beam following a location predicted by the 4D model based on the infra-red  
143 markers placed on the patient's abdominal wall. During irradiation, the tumour and the internal fiducials  
144 were monitored visually every second with EPID and the kV imagers. If the fiducial markers displaced  
145 from the predicted positions by 3 mm or more in 3 consecutive frames on the kV images, the irradiation  
146 was interrupted and rebuilding the 4D model was considered.

147

148 *Follow-up after treatment*

149 Follow-up visits were planned at 2, 4, 6, 9, and 12 months within the initial year after SBRT and every 3  
150 months thereafter. A CT scan was performed at each visit. The follow-up period was defined as the  
151 duration between the first day of treatment and the last follow-up visit or the date of death. Acute  
152 toxicity was defined as any treatment-related toxicities during the initial 6 months after the treatment.  
153 Toxicity grading was according to the Common Terminology Criteria for Adverse Events v.4.0.

154

155 **Results**

156 Twenty-two patients were enrolled into this study between August 2011 and July 2013. No patients  
157 experienced toxicities related to the insertion of fiducial markers. Twenty-two of the 101 inserted  
158 markers were coughed out before the CT simulation. Consequently, the number of remaining makers in  
159 4 patients decreased to two, which is insufficient for DTT to be performed. The planning procedures for  
160 DTT could not be performed in another two patients. One patient showed thoracic breathing that  
161 prevented the Vero system from tracking a tumour based on the abdominal motion (Supplementary Fig.  
162 2). In the other patient with histology-unproven primary lung cancer, the tumour spontaneously  
163 regressed during 10 days between the fiducial insertion and the simulation. For the remaining 16 patients,  
164 the CT simulation for DTT was successfully performed. Characteristics of the 16 patients are shown in  
165 Table 1.

166 The mean PTV volume reduced from 56.2 cm<sup>3</sup> to 39.6 cm<sup>3</sup> for the static and tracking plans, respectively  
167 (Table 2). GTV doses were not spoiled by the tracking method (dose covering 95% volume of GTV,  
168 93.4% vs. 93.7% of the prescription dose;  $p = 0.323$  by paired  $t$ -test). Doses to the normal lung and liver  
169 were reduced in the 16 patients. Lung V20, the relative volume receiving 20 Gy or more, was reduced by  
170 19.5%, from 5.5% to 4.4%. The tracking plan showed a higher maximal dose to the spinal cord than the

171 static plan in 5 patients. However, the difference did not exceed 0.3 Gy and was considered to be  
172 clinically acceptable.

173 The DTT irradiation was completed for all 64 fractions for the 16 patients. Mean and standard deviation  
174 in treatment time per fraction were 36.2 and 8.8 minutes (range, 19-70 minutes), respectively. The  
175 treatment time exceeded 50 minutes in 5 fractions because of communication failures between the  
176 tracking system and the gimbal system requiring a restart of the tracking procedure. The gold markers  
177 were well recognized with kV x-ray imagers throughout all treatment fractions. The 4D modelling was  
178 performed a mean of 1.9 times per fraction (range, 1 to 4).

179 With a median follow-up period of 13.2 months (range, 3.4–26.5 months), one patient experienced grade  
180 2 radiation pneumonitis. No severe toxicity grade 3 or worse has been observed in any of the patients.  
181 Two patients died of cancer, and one died of infectious pneumonia. Local tumour control was achieved  
182 except one patient who developed local recurrence at 12.0 months.

183

## 184 **Discussion**

185 The Vero4DRT system has two major advantages. The first is that tumour position can be monitored in  
186 real time using kV imagers and an EPID. The second is that no extra treatment time over static SBRT  
187 and no special training for breath control are needed for the 4D treatment, which is clinically beneficial

188 both for patient comfort and the throughput of the treatment system.

189 Several uncertainties are associated with 4D irradiation, including tumour position prediction errors and

190 mechanical errors in beam delivery, which are problems to be overcome. In the Vero4DRT, kV imagers

191 can ensure that the positions of the tumour and fiducial markers correspond to the predicted sites. EPID

192 can be used to verify the tumour position in complement to the kV imagers[21]. Furthermore, log files

193 allow retrospective confirmation of the accuracy in the delivery of tumour tracking after treatment. Our

194 previous study, which evaluated the initial 10 patients from the present study cohort, confirmed high

195 accuracies in the tracking performance. The 95th percentiles of overall tracking errors were 1.3 mm, 2.4

196 mm and 1.4 mm in left-right, cranio-caudal and anterior-posterior directions, respectively[22].

197 The Task Group 76 of the American Association of Physicists in Medicine classified motion

198 management methods into five types: motion-encompassing, respiratory gating, breath-hold, forced

199 shallow breathing with abdominal compression, and real-time tumour-tracking methods[8]. The

200 motion-encompassing method is the most conventional and well-established. However, it uses the largest

201 field of the five methods, with a large PTV. The breath-hold technique and abdominal compression are

202 not always suitable for frail and elderly patients. Respiratory gating needs a longer treatment time than

203 motion-encompassing methods. With a dynamic tracking method, patients do not need to hold or limit

204 their breath, and the tumour is always irradiated by the treatment beams without intermittence, leading to

205 a shorter treatment time than the breath-hold methods or the gating methods, and a comparable treatment  
206 time to the motion-encompassing methods. Dynamic tumour tracking is considered to be the favourable  
207 method among the five motion management methods from the patient compliance and comfort points of  
208 view. According to a Japanese survey of SBRT in 2009[23], the most frequent response regarding the  
209 time needed for a single daily fraction was 30 min, followed by 40 min. Our result of 36.2 min for a  
210 single fraction was thus comparable with standard times for SBRT in Japan. In addition to patient  
211 comfort, a few studies have suggested that prolongation of the treatment time for a single fraction may  
212 reduce its biological effectiveness[24,25]. Unfortunately, considerable prolongation of treatment time  
213 over 50 minutes occurred in 5 fractions in the present study. The cause for the prolongation was  
214 immaturity of the tracking system including software. To realize DTT irradiation, the tracking software  
215 needed to communicate with other systems in real time and to command several operations including  
216 control of the gimbal motion, process of signals from the infra-red camera and analysis of images from  
217 the kV x-ray imagers. The tracking system had initial instability in the communication process where the  
218 system could not simultaneously execute such different tasks. Some adaptations to the tracking system  
219 have been introduced after the present study with the aim of improving stability. Volumetric modulated  
220 arc therapy, which can reduce total MUs and consequently reduce treatment time, is being applied to  
221 SBRT for the lung[26]. Arc irradiation application to DTT is needed for reduction of treatment time with

222 the Vero4DRT. The Vero4DRT achieved the same level of geometric and dosimetric accuracy with  
223 conformal arc DTT irradiation as that with fixed-port DTT[27]. A treatment planning system capable of  
224 VMAT plan is under development for the Vero4DRT.

225 The disadvantages of the current Vero4DRT system are its dependence on 4D modeling and fiducial  
226 marker insertion. If no appropriate 4D model is acquired, dynamic tracking cannot be performed, as  
227 occurred in one patient. One solution for this issue is to track a tumour based on real-time stereo  
228 fluoroscopy without any 4D model. However, this method introduces another problem of skin doses due  
229 to the continuous fluoroscopy during a treatment time. Another way to improve the 4D model is a  
230 training to encourage for patients to perform periodical abdominal breathing[28].

231 The Vero4DRT currently requires fiducial markers with x-ray fluoroscopy monitoring to detect the  
232 tumour position and create the 4D model. Two types of fiducials are applicable to the Vero4DRT: one is  
233 a spherical marker, and the other is a cylindrical marker. We used the spherical gold markers that were  
234 inserted into a peripheral bronchiole under bronchoscopy. This method was reported in more detail by  
235 Imura et al. from Hokkaido University[29]. All 57 patients in their report tolerated the marker  
236 implantation procedure and only one experienced pneumothorax, which resolved with bed rest. The  
237 toxicity rate was much lower than those of percutaneous insertion methods[30,31]. Trade-offs, however,  
238 for the reduced toxicity are marker dislocation between insertion and radiotherapy, and positional

239     uncertainty between the tumour and makers. Imura et al. reported that 25% of the inserted markers could  
240     not be detected throughout the treatment period. Indeed, 22% of the markers in this study were coughed  
241     out before the CT simulation, and 4 of 22 (18%) patients could not undergo the DTT due to the marker  
242     dislocation. The reason why the Vero4DRT system requires 3 markers or more in the use of spherical  
243     markers is to detect the marker dislocation. Regarding the positional uncertainty between the tumour and  
244     markers, Ueki et al. evaluated intra- and interfractional variations[19]. Root mean squares in the  
245     intrafractional variations were 0.6 mm, 0.9 mm and 1.5 mm in the right-left, anteroposterior and  
246     craniocaudal directions, respectively. Moderate correlations of the intrafractional variation with tumour  
247     motion amplitude and tumour-marker distance were observed with correlation coefficients of 0.549–  
248     0.780. However, the intrafractional error did not always distribute symmetrically around zero, but often  
249     distributed in one side above or below zero. The direction and amplitude of the intrafractional variations  
250     varied between patients. Base on the results, we judged that a uniform isotropic margin was inadequate  
251     to cover the intrafractional variations, and that the fused CT approach as in the Method section was  
252     suitable for DTT planning. The interfractional variation could be covered by a 2.5-mm margin.

253     In conclusion, DTT radiotherapy with real-time monitoring using a gimbal mounted linac was clinically  
254     feasible for the lung without any severe acute toxicity.

255



256     **Conflict of interests:**

257     T.M., M.K. and M.H. have consultancy agreements with Mitsubishi Heavy Industries Ltd., Japan. A  
258     sponsored research program is provided by Mitsubishi Heavy Industries Ltd.

259

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265

266

267     **References**

268     [1]     Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.

269     [2]     Foundation for Promotion of Cancer Research. Cancer Statistics in Japan-2013 Available at:  
270     [http://ganjoho.jp/pro/statistics/en/backnumber/2013\\_en.html](http://ganjoho.jp/pro/statistics/en/backnumber/2013_en.html). Accessed January 10, 2014.

271     [3]     Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese lung cancer  
272     registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J  
273     Thorac Oncol 2011;6:1229–35.

- 274 [4] Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small  
275 cell lung cancer: a National Cancer Database survey. *J Thorac Oncol* 2010;5:29–33.
- 276 [5] Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body  
277 radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–6.
- 278 [6] Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Stereotactic Body  
279 Radiation Therapy For T1N0M0 Non-small Cell Lung Cancer: First Report for Inoperable Population  
280 of a Phase II Trial by Japan Clinical Oncology Group (JCOG 0403). *Int J Radiat Oncol Biol Phys*  
281 2012;84:S46.
- 282 [7] Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. A Phase II Trial of  
283 Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-small Cell Lung Cancer: Japan  
284 Clinical Oncology Group (JCOG0403). *Int J Radiat Oncol Biol Phys* 2010;78:S27–8.
- 285 [8] Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, et al. The management of  
286 respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874–  
287 900.
- 288 [9] Matsuo Y, Shibuya K, Nakamura M, Narabayashi M, Sakanaka K, Ueki N, et al. Dose-volume  
289 metrics associated with radiation pneumonitis after stereotactic body radiation therapy for lung cancer.  
290 *Int J Radiat Oncol Biol Phys* 2012;83:e545–9.
- 291 [10] Guckenberger M, Baier K, Polat B, Richter A, Krieger T, Wilbert J, et al. Dose-response relationship  
292 for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother Oncol*  
293 2010;97:65–70.
- 294 [11] Borst GR, Ishikawa M, Nijkamp J, Hauptmann M, Shirato H, Bengua G, et al. Radiation pneumonitis  
295 after hypofractionated radiotherapy: evaluation of the LQ(L) model and different dose parameters. *Int*  
296 *J Radiat Oncol Biol Phys* 2010;77:1596–603.
- 297 [12] Kamino Y, Takayama K, Kokubo M, Narita Y, Hirai E, Kawawda N, et al. Development of a  
298 four-dimensional image-guided radiotherapy system with a gimbaled X-ray head. *Int J Radiat Oncol*  
299 *Biol Phys* 2006;66:271–8.

- 300 [13] Mukumoto N, Nakamura M, Sawada A, Takahashi K, Miyabe Y, Takayama K, et al. Positional  
301 accuracy of novel x-ray-image-based dynamic tumor-tracking irradiation using a gimbaled MV x-ray  
302 head of a Vero4DRT (MHI-TM2000). *Med Phys* 2012;39:6287–96.
- 303 [14] Mukumoto N, Nakamura M, Sawada A, Suzuki Y, Takahashi K, Miyabe Y, et al. Accuracy  
304 verification of infrared marker-based dynamic tumor-tracking irradiation using the gimbaled x-ray  
305 head of the Vero4DRT (MHI-TM2000). *Med Phys* 2013;40:041706.
- 306 [15] Depuydt T, Verellen D, Haas O, Gevaert T, Linthout N, Duchateau M, et al. Geometric accuracy of a  
307 novel gimbals based radiation therapy tumor tracking system. *Radiother Oncol* 2011;98:365–72.
- 308 [16] Nakamura M, Sawada A, Ishihara Y, Takayama K, Mizowaki T, Kaneko S, et al. Dosimetric  
309 characterization of a multileaf collimator for a new four-dimensional image-guided radiotherapy  
310 system with a gimbaled x-ray head, MHI-TM2000. *Med Phys* 2010;37:4684–91.
- 311 [17] Takayama K, Mizowaki T, Kokubo M, Kawada N, Nakayama H, Narita Y, et al. Initial validations  
312 for pursuing irradiation using a gimbals tracking system. *Radiother Oncol* 2009;93:45–9.
- 313 [18] Matsuo Y, Takayama K, Nagata Y, Kunieda E, Tateoka K, Ishizuka N, et al. Interinstitutional  
314 variations in planning for stereotactic body radiation therapy for lung cancer. *Int J Radiat Oncol Biol*  
315 *Phys* 2007;68:416–25.
- 316 [19] Ueki N, Matsuo Y, Nakamura M, Mukumoto N, Iizuka Y, Miyabe Y, et al. Intra- and interfractional  
317 variations in geometric arrangement between lung tumours and implanted markers. *Radiother Oncol*  
318 2014;110:523–8.
- 319 [20] Ishihara Y, Sawada A, Nakamura M, Mukumoto N, Kaneko S, Takayama K, et al. Development of  
320 Monte Carlo Dose Calculation System for Tumor-Tracking Irradiation with a Gimbaled X-Ray Head.  
321 *Med Phys* 2011;38:3644.
- 322 [21] Poels K, Depuydt T, Verellen D, Engels B, Collen C, Heinrich S, et al. A complementary  
323 dual-modality verification for tumor tracking on a gimbaled linac system. *Radiother Oncol*  
324 2013;109:469–74.

- 325 [22] Mukumoto N, Nakamura M, Yamada M, Takahashi K, Tanabe H, Yano S, et al. Intrafractional  
326 tracking accuracy in infrared marker-based hybrid dynamic tumour-tracking irradiation with a  
327 gimballed linac. *Radiother Oncol* 2014;111:301–5.
- 328 [23] Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, et al. Survey of stereotactic  
329 body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. *Int*  
330 *J Radiat Oncol Biol Phys* 2009;75:343–7.
- 331 [24] Fowler JF, Welsh JS, Howard SP. Loss of biological effect in prolonged fraction delivery. *Int J Radiat*  
332 *Oncol Biol Phys* 2004;59:242–9.
- 333 [25] Shibamoto Y, Otsuka S, Iwata H, Sugie C, Ogino H, Tomita N. Radiobiological evaluation of the  
334 radiation dose as used in high-precision radiotherapy: effect of prolonged delivery time and  
335 applicability of the linear-quadratic model. *J Radiat Res* 2012;53:1–9.
- 336 [26] Verbakel WF a R, Senan S, Cuijpers JP, Slotman BJ, Lagerwaard FJ. Rapid delivery of stereotactic  
337 radiotherapy for peripheral lung tumors using volumetric intensity-modulated arcs. *Radiother Oncol*  
338 2009;93:122–4.
- 339 [27] Ono T, Miyabe Y, Yamada M, Shiinoki T, Sawada A, Kaneko S, et al. Geometric and dosimetric  
340 accuracy of dynamic tumor-tracking conformal arc irradiation with a gimbaled x-ray head. *Med Phys*  
341 2014;41:031705.
- 342 [28] Nakamura M, Sawada A, Mukumoto N, Takahashi K, Mizowaki T, Kokubo M, et al. Effect of audio  
343 instruction on tracking errors using a four-dimensional image-guided radiotherapy system. *J Appl*  
344 *Clin Med Phys* 2013;14:255–64.
- 345 [29] Imura M, Yamazaki K, Shirato H, Onimaru R, Fujino M, Shimizu S, et al. Insertion and fixation of  
346 fiducial markers for setup and tracking of lung tumors in radiotherapy. *Int J Radiat Oncol Biol Phys*  
347 2005;63:1442–7.
- 348 [30] Kothary N, Heit JJ, Louie JD, Kuo WT, Loo BW, Koong A, et al. Safety and efficacy of percutaneous  
349 fiducial marker implantation for image-guided radiation therapy. *J Vasc Interv Radiol* 2009;20:235–9.

350 [31] Hong JC, Yu Y, Rao AK, Dieterich S, Maxim PG, Le Q-T, et al. High retention and safety of  
351 percutaneously implanted endovascular embolization coils as fiducial markers for image-guided  
352 stereotactic ablative radiotherapy of pulmonary tumors. Int J Radiat Oncol Biol Phys 2011;81:85–90.

353

354 **Figure legend:**

355 **Supplementary figure 1. A schema for definition of an internal target volume (ITV) for**  
356 **tracking**

357 a) An example of intrafractional change in alignment of gross tumour volume (GTV) and  
358 fiducial markers, and intrafractional tumour deformation.

359 b) Definition of ITV for tracking. The GTVs are fused based on the marker centroids. Then,  
360 an ITV for tracking (the thick red line) is defined as a composite of the fused GTVs.

361 c) A screenshot from a case. Several lines with various colours are shown around the  
362 tumour, which indicate GTVs from phase images of 4D CT. An ITV (not shown) is defined as  
363 a volume including all the GTVs. The outermost pink line indicates a planning target  
364 volume for the ITV.

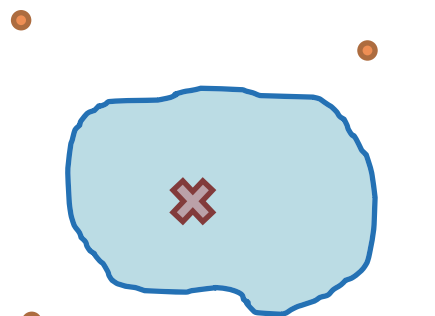
365

366 **Supplementary figure 2. A patient who showed thoracic breathing**

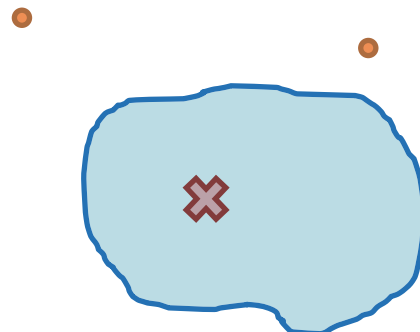
367 The tumour position in the superior-inferior (SI) direction and the abdominal wall position  
368 in the anterior-posterior (AP) direction are shown in blue and red lines, respectively. Note  
369 that the patient showed thoracic breathing where the tumour moved without any  
370 abdominal motion during the initial 10 seconds. Thoracic breathing was the dominant  
371 respiratory pattern in the patient so that the Vero system could not create an appropriate  
372 4D model for the patient.

caudal <-- respiratory motion --> cranial

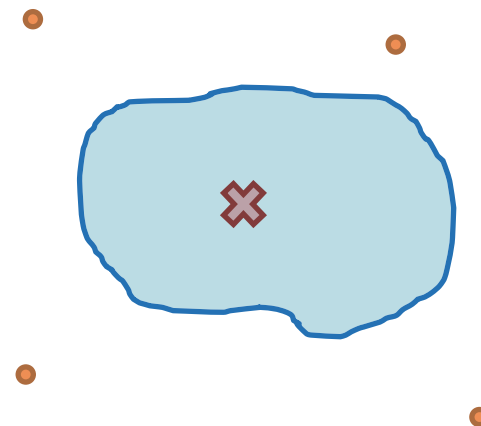
a)



exhale

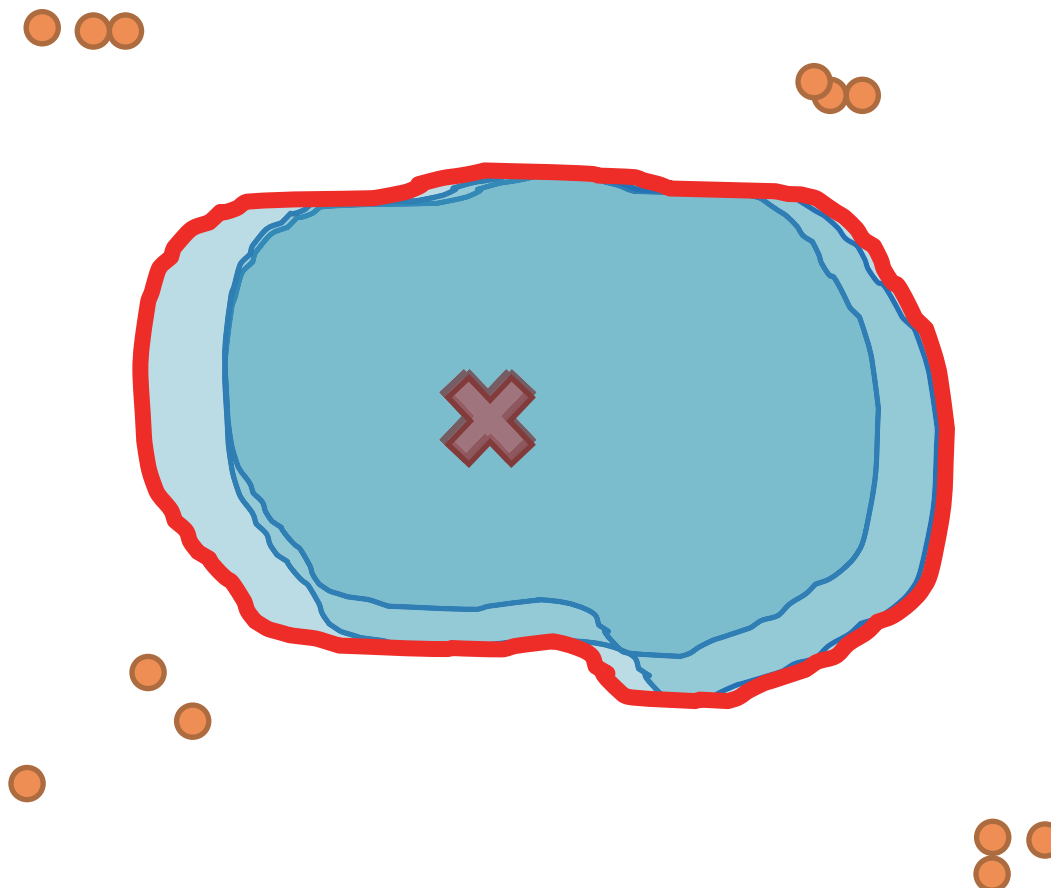


mid-inhale



end-inhale

- fiducial markers
- ✕ centroid of markers
- GTV



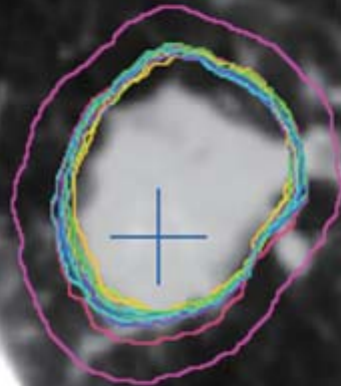
b)



Axial View

R

L



P

c)

4-D Series



